REVIEW

Embolic Stroke of Undetermined Source

New Data and New Controversies on Cardiac Monitoring and Anticoagulation

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Abstract

Embolic strokes of undetermined source (ESUS) represent 9%–25% of all ischemic strokes. Based on the suspicion that a large proportion of cardioembolic sources remain undetected among embolic stroke of undetermined source patients, it has been hypothesized that a universal approach of anticoagulation would be better than aspirin for preventing recurrent strokes. However, 4 randomized controlled trials (RCTs), with different degrees of patient selection, failed to confirm this hypothesis. In parallel, several RCTs consistently demonstrated that prolonged cardiac monitoring increased atrial fibrillation detection and anticoagulation initiation compared with usual care in patients with ESUS, and later in individuals with ischemic stroke of known cause (e.g., large or small vessel disease). However, none of these trials or subsequent meta-analyses of all available RCTs have shown a reduction in stroke recurrence associated with the use of prolonged cardiac monitoring. In this article, we review the clinical and research implications of recent RCTs of antithrombotic therapy in patients with ESUS and in high-risk populations with and without stroke, with device-detected asymptomatic atrial fibrillation.

The ESUS Concept and the Failure of Anticoagulants to Prevent Stroke Recurrence

In 2014, the concept of embolic strokes of undetermined source (ESUS) was introduced to provide a pragmatic approach to the diagnosis and management of ischemic stroke in patients with a suspected but unidentified embolic source.[1] ESUS was defined as a nonlacunar stroke detected using neuroimaging of the brain, in the absence of extracranial or intracranial atherosclerosis causing ≥50% stenosis in arteries supplying the area of ischemia, without a high-risk cardioembolic source of embolism, and no other specific cause of stroke.[1] The main rationale behind the ESUS concept was that various heterogeneous underlying causes of stroke, such as cardioembolic sources and artery-to-artery sources, would all respond favorably to anticoagulation. The introduction of the ESUS concept was followed by 2 large randomized controlled trials (RCTs), New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Acetylsalicylic Acid to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS)[2] and Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS).[3]

The NAVIGATE ESUS trial compared rivaroxaban (15 mg once daily) with aspirin (100 mg once daily) in patients who had an ESUS between 7 days and 6 months before screening (Table 1).[2] The trial was prematurely ended due to the absence of stroke risk reduction and

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Glossary

AF = atrial fibrillation; **AFDAS** = AF detected after stroke; **AHRE** = atrial high-rate episode; **ARCADIA** = Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke; **ARTESIA** = Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation; **ATTICUS** = Apixaban for treatment of embolic stroke of undetermined source; **AVERROES** = Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; **DOAC** = direct oral anticoagulant; **ESUS** = embolic strokes of undetermined source; **HR** = hazard ratio; **ICM** = implantable cardiac monitor; **LA** = left atrial; **MOSES** = Midregional Proatrial Natriuretic Peptide to Guide Secondary Stroke Prevention; **MR-pANP** = midregional proANP; **NAVIGATE ESUS** = New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Acetylsalicylic Acid to Prevent Embolism in Embolic Stroke of Undetermined Source; **NOAH-AFNET 6** = Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; **NT-proBNP** = N-terminal pro-B-type natriuretic peptide; **PCM** = prolonged cardiac monitoring; **RCT** = randomized controlled trial; **RE-SPECT ESUS** = Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source; **RR** = relative risk; **SCAF** = subclinical atrial fibrillation; **TIA** = transient ischemic attack; **WARSS** = Warfarin-Aspirin Recurrent Stroke Study.

an excess bleeding risk among patients assigned to rivaroxaban. The primary efficacy outcome of recurrent stroke of any type or systemic embolism occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and 160 patients in the aspirin group (annualized rate 4.8%) (hazard ratio [HR] 1.07, 95% CI 0.87–1.33). There were no differences in the risk of ischemic stroke between groups, and major bleeding and intracranial hemorrhage rates were significantly higher in the rivaroxaban group than in the aspirin group (Table 2).

The RE-SPECT ESUS trial aimed to assess the effectiveness and safety of the oral thrombin inhibitor dabigatran etexilate 150 mg or 110 mg twice daily compared with aspirin 100 mg in preventing secondary strokes in patients with ESUS.[3] There were no differences in the primary outcome of any type of recurrent stroke (HR 0.85, 95% CI 0.69–1.03) or major hemorrhage (Table 2) between groups. The primary outcome, any type of recurrent stroke, occurred in 177 patients in the dabigatran group (annualized rate of 4.1%) compared with 207 patients in the aspirin group (annualized rate of 4.8%).[3] There were no differences in ischemic stroke risk (Table 2) or intracranial hemorrhage (HR 0.98, 95% CI 0.60–1.60).[3]

Notably, the disparity between the 2 trials regarding safety outcomes stemmed from the bleeding risk, which was more pronounced among patients assigned to aspirin than those on oral anticoagulants such as rivaroxaban and dabigatran. Although the incidences of major bleeding were comparable between the rivaroxaban and dabigatran groups, the occurrence of major bleeding in patients assigned aspirin in the NAVIGATE ESUS trial was only half the risk observed in patients assigned aspirin in the RE-SPECT ESUS trial. The reason behind this variation in major bleeding outcomes remains uncertain. It could be attributed to differences in the formulation of aspirin, with enteric-coated and plain forms being used in the NAVIGATE ESUS and RE-SPECT ESUS trials, respectively, or it might simply be a result of random chance.[4]

In a systematic review and meta-analysis of the NAVIGATE-ESUS and RE-SPECT ESUS trials, anticoagulation with either dabigatran or rivaroxaban compared with aspirin did not reduce the risk of recurrent stroke (relative risk [RR] 0.96, 95% CI 0.76–1.20) or increase major bleeding (RR 1.77, 95% CI 0.80–3.89).[5] However, anticoagulation significantly increased the composite of major or clinically relevant nonmajor bleeding (RR 1.57, 95% CI 1.26–197).[5] There was no reduction in any of the secondary efficacy outcomes, including ischemic stroke, myocardial infarction, and all-cause mortality.[5] The validity of the results of this study-level meta-analysis is limited given that it was only based on 2 trials.

Defining Atrial Cardiopathy as a Stroke Recurrence Prevention Target in ESUS Trials

Given the challenges and limitations faced in NAVIGATE ESUS and RE-SPECT ESUS trials, and the frustration experienced by ESUS appearing strokes that recur at a rate of 4.0%–4.7% per year,[2,3] researchers have continued to explore alternative approaches and potential targets for stroke prevention in patients with ESUS.[6]

The potential cardioembolic sources initially originally thought most likely to be causal in ESUS were covert AF and atrial cardiopathy, which includes left atrial (LA) atrial remodeling (e.g., enlargement, fibrosis), slow LA appendage flow, and subclinical damage to endothelial cells and cardiomyocytes.[7] Atrial dysfunction and remodeling, irrespective of the presence of AF, have been proven to be a substrate for LA thrombogenesis and embolism.[8-10] Furthermore, a prespecified subanalysis of the NAVIGATE ESUS trial suggested that rivaroxaban was associated with a lower risk of stroke

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Table 1 Baseline Characteristics of Recent AHRE/SCAF, AF, and ESUS Trials

	NOAH	ARTESIA	AVERROES	ARISTOTLE	RE-LY	ROCKET AF	ENGAGE AF	NAVIGATE	RE-SPECT	ARCADIA	ATTICUS
Cohort type	AHRE/ SCAF	AHRE/ SCAF	AF	AF	AF	AF	AF	ESUS	ESUS	ESUS + AC	Enriched ESUS[a]
Sample size, n	2,536	4,012	5,599	18,201	18,113	14,264	14,071	7,213	5,390	1,015	352
Follow-up, m	21, median	42, mean	13, mean	22, median	24, median	23, median	34, median	11, median	19, median	22, median	12, total
Age, median or mean	77.5 ± 6.7	76.8 ± 7.6	70.0 ± 9.0	70 (63–76)	71.5 ± 8.7	73 (65–78)	72 (64–78)	66.9 ± 9.8	64.2 ± 11.2	68.0 ± 10.9	68.4 ± 10.5
Female sex, %	37.4	36.1	41.5	35.0	36.4	39.7	37.7	38.5	36.9	54.3	48.6
Hypertension	86.9	81.5	86.4	87.4	78.9	90.5	93.7	77.4	73.9	77.2	86.1
Diabetes	26.9	29.1	19.6	25.0	23.3	39.9	36.1	25.0	22.7	31.0	28.3
Prior stroke/TIA	10.0	NR	13.6	NR	20.0	NR	28.2	17.5	18.1	19.4	15.3
Prior stroke/TIA/SE	NR	9.0	NR	19.4	NR	54.8	NR	NR	NR	NR	NR
Atrial fibrillation/flutter	100.0	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0
Heart failure	27.4	28.3	38.8	35.4	32.0	62.5	57.9	6.6	4.5	7.0	2.0
Prior myocardial infarction	NR	NR	NR	14.2	16.6	17.3	NR	3.3	6.3	NR	3.1
Ischemic heart disease	26.4	37.0	NR	NR	NR	NR	NR	6.6	10.7	10.2	8.1
CHA^2DS^2-VASc score	4 (3–5)	3 (3–4)	NR	NR	NR	NR	NR	≥2	≥2	≥2	5 (4–6)
$CHADS_2$	NR	NR	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	3.5 ± 0.9	2.8 ± 1.0	≥2	≥2	≥2	≥4

Abbreviations: AC = atrial cardiopathy; AHRE = atrial high-rate episodes; CVE = cerebrovascular event; ESUS = embolic stroke of undetermined source; NR = not reported; SCAF = subclinical atrial fibrillation; SE = systemic embolism; TIA = transient ischemic attack.
Ischemic heart disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting in NOAH-AFNET. Data for ENGAGE-AF TIMI-48 trial include patients from the high-dose edoxaban and warfarin arms.
[a] Enriched ESUS definition of ≥1 clinical, electrocardiographic, or echocardiographic criterion predictive of atrial fibrillation (CHA^2DS^2-VASc score ≥4; AHRE ≥20 premature atrial complexes with an accelerated cycle length lasting <30 seconds; left atrial diameter >45 mm, spontaneous echo contrast, or left atrial appendage flow velocity ≤0.2 m/s).

recurrence than aspirin in patients with an LA diameter ≥4.6 cm (HR 0.26, 95% CI 0.07–0.94).[11]

The concept of atrial cardiopathy constitutes a continuum, with cardiopathy in the setting of overt AF representing only the tip of iceberg. Although a full review of the potential sources of atrial cardiopathy is outside of the scope of this article, some of the most important and consistent markers used to define this concept have included P-wave abnormalities, natriuretic peptides, and LA enlargement, as discussed below.

P-Wave Abnormalities

P-wave markers of LA dysfunction, including prolonged P-wave duration, advanced interatrial block, and increased P-wave terminal on lead V1, are independently associated with advanced atrial disease, covert AF, and ischemic stroke.[12,13]

Natriuretic Peptides

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the N-terminal inactive protein cleaved from the brain natriuretic peptide and is released mostly from the ventricular cardiomyocytes in response to stretching by increased ventricular blood volume. By contrast, midregional proANP (MR-proANP) is released from atrial cardiomyocytes and has been associated with newly diagnosed AF in 3 independent, prospective cohorts of patients with an acute ischemic stroke.[14-16] In the largest cohort, MR-proANP was also associated with the risk of major adverse cardiovascular events, including recurrent stroke (adjusted subdistributional HR 2.02, 95% CI 1.32–3.08).[16] As such, rather than NT-proBNP, MR-proANP may be a more reliable marker of atrial cardiopathy as well as undetected AF, and thus, possibly of patients benefiting from oral anticoagulation. In an analysis from the Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial, patients with increased NT-proBNP serum levels but without known AF had a lower risk of stroke recurrence when randomized to warfarin rather than aspirin.[17]

LA Enlargement

Although LA enlargement often coexists with AF, people in sinus rhythm with an enlarged LA also have an increased risk of stroke (HR 1.63, 95% 1.08–2.46).[18] Regarding sex differences, Chinese women—but not men—with an enlarged LA had an increased risk of stroke (RR 2.44, 95% CI 1.11–5.36).[19] However, the opposite was found in other important epidemiologic studies.[20]

Based on the available evidence, atrial cardiopathy became a new target for stroke prevention with anticoagulation in patients with ESUS and led to the design of 3 additional RCTs.

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Table 2 Annualized Event Rates in Recent AHRE/SCAF, AF, and ESUS Trials

	Study arms		Ischemic stroke						Major bleeding					
	Intervention	Control	DOAC		Control				DOAC		Control			
Study			n/N	AR	n/N	AR	HR	95% CI	n/N	AR	n/N	AR	HR	95% CI
AHRE/SCAF														
NOAH-AFNET	Edoxaban	ASA/placebo	22/1,270	0.90	27/1,266	1.10	0.79	0.45–1.39	53/2,534	2.10	25/2,508	1.00	2.10	1.30–3.38
ARTESIA	Apixaban	ASA	45/2,015	0.64	71/1,997	1.02	0.62	0.43–0.91	86/1,989	1.71	47/1,972	0.94	1.80[a]	1.26–2.57
AF														
AVERROES	Apixaban	ASA	35/2,808	1.10	93/2,791	3.00	0.37	0.25–0.55	44/2,808	1.40	39/2,791	1.20	1.13	0.74–1.75
ARISTOTLE	Apixaban	VKA	162/9,120	0.97	175/9,081	1.05	0.92	0.74–1.13	327/9,088	2.13	462/9,052	3.09	0.69	0.60–0.80
RE-LY 110 mg	Dabigatran	VKA	159/6,015	1.34	142/6,022	1.20	1.11	0.89–1.40	322/6,015	2.71	397/6,022	3.36	0.80	0.69–0.93
RE-LY 150 mg	Dabigatran	VKA	111/6,076	0.92	142/6,022	1.20	0.76	0.60–0.98	375/6,076	3.11	397/6,022	3.36	0.93	0.81–1.07
ROCKET AF	Rivaroxaban	VKA	149/7,111	1.34	386/7,125	1.42	0.94	0.75–1.17	395/7,111	5.60	386/7,125	5.40	1.04	0.90–1.20
ENGAGE AF	Edoxaban	VKA	236/7,035	1.25	235/7,036	1.25	1.00	0.83–1.19	418/7,012	2.75	524/7,012	3.43	0.80	0.71–0.91
AF + prior CVE														
AVERROES	Apixaban	ASA	9/390	2.12	27/374	7.46	0.33	0.15–0.69	14/390	4.10	11/374	2.89	1.28	0.58–2.82
ARISTOTLE	Apixaban	VKA	57/9,120	1.92	68/9,081	2.23	0.86	0.60–1.22	77/9,120	2.84	106/9,081	3.91	0.73	0.55–0.98
RE-LY 110 mg	Dabigatran	VKA	52/1,195	2.19	41/1,195	1.75	1.26	0.84–1.90	65/1,195	2.74	97/1,195	4.15	0.66	0.48–0.90
RE-LY 150 mg	Dabigatran	VKA	43/1,233	1.75	41/1,195	1.75	1.00	0.65–1.54	102/1,233	4.15	97/1,195	4.15	1.01	0.77–1.06
ROCKET AF	Rivaroxaban	VKA	151/3,754	2.34	144/3,714	2.27	0.88	0.64–1.21	178/3,754	3.13	183/3,714	3.22	0.97	0.79–1.19
ENGAGE AF	Edoxaban	VKA	105	2.04	109	2.13	0.96	0.73–1.25	138	3.25	167	3.86	0.84	0.67–1.06
ESUS														
NAVIGATE	Rivaroxaban	ASA	158/3,609	4.70	156/3,604	4.70	1.01	0.81–1.26	62/3,609	1.80	23/3,604	0.70	2.72	1.68–4.39
RE-SPECT	Dabigatran	ASA	172/2,695	4.00	203/2,695	4.70	0.84	0.68–1.03	77/2,695	1.70	64/2,695	1.40	1.19	0.85–1.66
ARCADIA	Apixaban	ASA	37/507	4.10	37/508	4.40	1.00	0.64–1.55	5/482	0.70	5/493	0.80	1.02	0.63–3.74
ATTICUS	Apixaban	ASA	11/178	5.70	12/174	5.90	0.88	0.39–1.99	1/178	0.60	1/174	1/174	0.95	0.06–14.8

Abbreviations: AR = absolute risk; ASA = aspirin; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonists.
Annualized rates were reported for NOAH-AFNET, ARTESIA, ARISTOTLE, RE-LY, ENGAGE-AF TIMI-48, NAVIGATE ESUS, RE-SPECT ESUS, ARCADIA, and ATTICUS. Rates at the first 12 months were reported for AVERROES. Data for ENGAGE-AF TIMI-48 trial include patients from the high-dose edoxaban and warfarin arms. Relative risks are reported for the RE-LY study instead of hazard ratios.
[a] On treatment population.

Clinical Trials of Anticoagulation vs Aspirin in Patients With ESUS and Atrial Cardiopathy

The ATTICUS (apixaban for treatment of embolic stroke of undetermined source) trial enrolled patients with ESUS at a median of 8 days after symptom onset, with at least one of ≥1 clinical, electrocardiographic, or echocardiographic criterion predictive of atrial fibrillation (AF) (CHA^2DS^2-VASc score ≥4; atrial high-rate episodes [AHREs] ≥20 premature atrial complexes with an accelerated cycle length lasting <30 seconds; LA diameter >45 mm, spontaneous echo contrast, or LA appendage flow velocity ≤0.2 m/s).[21] An implantable cardiac monitor (ICM) was applied before study inclusion in 95.4% of the cohort, and the reminder received an external loop recorder. ATTICUS was a randomized, open-label study aimed to determine whether apixaban (5 mg twice daily; 2.5 mg twice daily in patients with a creatinine clearance of 15–29 mL/min or with at least 2 of the following 3 factors: age ≥80 years or body weight ≤60 kg or serum creatinine ≥1.5 mg/dL) was superior to aspirin (100 mg once daily) in preventing new ischemic lesions at 12 months of follow-up as assessed using magnetic resonance imaging in selected adult (≥18 years) patients with recent ESUS.[21] Patients in the aspirin group were switched to apixaban upon diagnosis of AF on cardiac monitoring. Recruitment was stopped after an interim analysis because of futility. The primary efficacy outcome was new ischemic lesion on diffusion-weighted or fluid-attenuated inversion recovery brain MRI relative to the baseline MRI at 12 months of follow-up. Enrollment was

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stopped due to futility based on the recommendation of the data safety monitoring board on August 5, 2020. The follow-up of already enrolled patients continued as planned because there were no safety concerns. Overall, 352 patients were included, 178 and 174 patients in the apixaban and aspirin arms, respectively. ATTICUS did not demonstrate a superiority of apixaban compared with aspirin for preventing the primary efficacy outcome: 23 of 169 (13.6%) in the apixaban arm vs 25 of 156 in the aspirin group (16.0%), adjusted OR 0.79, 95% CI 0.42–1.48.[21] There were no differences in recurrent ischemic stroke or major hemorrhage between groups (Table 2). There were no intracranial hemorrhages in either arm. AF was newly detected in 40 participants in the apixaban group (22.5%) and 49 in the aspirin arm (28.2%). Older patients aged ≥75 years may, however, benefit from anticoagulation, as suggested in an interaction analysis.[21]

ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) was a biomarker-driven, randomized, double-blind, active-control, clinical trial testing the hypothesis that apixaban is superior to aspirin in preventing recurrent strokes in patients with ESUS and study-defined atrial cardiopathy.[22] The study population consisted of patients aged ≥45 years with ESUS and evidence of atrial cardiopathy, defined as ≥1 of the following markers: P-wave terminal force >5,000 μV·ms in ECG lead V1, serum NT-proBNP >250 pg/mL, and LA diameter index ≥3 cm/m^2 on echocardiogram.[22] Patients were randomized within 180 days poststroke to apixaban 5 mg twice daily (2.5 mg twice daily in participants who meet 2 or more of the standard dose-adjustment criteria: age ≥80 years, weight ≤60 kg, or creatinine ≥1.5 mg/dL) or aspirin 81 mg once daily. The primary efficacy outcome was recurrent stroke of any type, and the primary safety outcomes were symptomatic intracranial hemorrhage and major hemorrhage other than intracranial hemorrhage. The rate of stroke recurrence between apixaban and aspirin arms was the same (4.4% in both arms, HR 1.00, 95% CI 0.64–1.55). The risk of ischemic stroke (Table 2), major hemorrhage (Table 2), and death (1.8% apixaban vs 1.2% aspirin) was statistically similar between treatment arms. Symptomatic intracerebral hemorrhage was significantly more frequent in the aspirin group (0% apixaban vs 1.1% aspirin, risk difference −1.1, 95% CI −1.8 to −0.3), possibly explained by chance related to the low number of events.[22]

Limitations in the Echocardiographic Search of Cardioembolic Sources Related to the ESUS Definition

The echocardiographic diagnostic workup recommended in the original ESUS editorial was transthoracic echocardiography, whereas transesophageal echocardiography was discouraged.[1] The sensitivity of transthoracic echocardiography for detecting LA appendage thrombi is close to zero. The left ventricle is positioned close to the anterior thoracic wall, and thus, physicians treating patients with stroke tend to believe that the sensitivity of transthoracic echocardiography for detecting left ventricular thrombi is high. However, the reported sensitivity of transthoracic echocardiography compared with cardiac MRI is only 64% when using contrast and as low as 35% when intravenous ultrasound contrast is not used.[23] Newer approaches such as extended CT angiograms including the LA appendage have demonstrated the presence of intracardiac thrombi or slow LA appendage flow in up to 6.5%–13.5% of patients with ischemic stroke.[24-27] The DAYLIGHT (Extended Computed Tomography Angiography for the Successful Diagnosis of Cardioaortic Thrombus in Acute Ischemic Stroke and TIA) trial, a single-center RCT, compares the use of extended (6 cm below the carina) CT angiography vs standard CT angiography plus usual stroke workup for the detection of intracardiac thrombi in patients with acute ischemic stroke and transient ischemic attack (TIA) (NCT05522244). Based on its potentially easy adoption, rapid implementation, and the lack of significant complications (e.g., nonsignificant excess radiation or contrast), extended CT angiography is likely to be adopted in the future, further reducing the proportion of patients with ESUS and making the remaining patients with ESUS less likely to benefit from anticoagulation than antiplatelet therapy.

Implications of the ESUS Definition on AF Screening Poststroke

Considering the neutral findings of ARCADIA and 3 previous ESUS trials, poststroke cardiac monitoring has regained a critical role in the realm of secondary stroke prevention strategies. Given the lack of evidence supporting the one-size-fits-all approach for anticoagulation in patients with ESUS, it is now crucial to understand who, why, when, and for how long patients should be monitored after an ischemic stroke or TIA of undetermined cause.

The ESUS definition required ≥24-hour cardiac monitoring with automated rhythm detection (cardiac telemetry was insufficient).[1] However, 24 hours of cardiac monitoring has a low AF detection yield and leaves a substantial proportion of patients with AF undiagnosed. The diagnostic yield of 24-hour Holter for AF in patients with stroke is approximately 5%,[28] whereas detection rates of AF using prolonged cardiac monitoring (PCM) with ICM in patients with ESUS can be as high as 16.4% at 3 months, 22.0% at 6 months, 22.1% at 1 year, and 24.8% at 2 years.[29] In NAVIGATE ESUS, the median duration of cardiac monitoring before randomization was 24 hours, and only 34% of study participants received ≥48 hours of monitoring.[2] Among 7,213 participants, 239 (3.13%) were newly diagnosed with AF during follow-up, and 228 (95% of patients with a new AF diagnosis) were started on anticoagulants.[11] In RE-SPECT ESUS, 403 of 5,390 patients (7.5%) were diagnosed with AF during follow-up.[30] Of 101 patients with available information on AF burden, the arrhythmia lasted ≤6 minutes in 43% and >6 minutes in the remaining

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57%.[3,30] Data on duration of cardiac monitoring before enrollment have not been published for the ATTICUS or ARCADIA trials yet. However, the duration of monitoring required for both trials before randomization was similar to that of the NAVIGATE and RE-SPECT ESUS trials.

It is well known that the duration of cardiac monitoring in patients with stroke is directly associated with AF burden and the resulting embolic risk. In other words, short-duration monitoring mainly detects high-burden AF, whereas longer-duration monitoring can detect both high-burden and low-burden AF.[31] The latter concept is important because, along with other factors (e.g., LA size, age, sex), AF burden determines its embolic risk. The larger the burden, the higher the risk of stroke recurrence.[32] It has been shown that AF detected after stroke (AFDAS) is associated with a 26% lower risk of stroke recurrence than AF already known before stroke onset.[33] This is probably related to the fact that AF known before stroke occurrence is usually detected on 12-lead ECGs and is, therefore, high burden, whereas AFDAS, according to its definition,[34] is always found after short or PCM and has a lower burden.[35] In addition, patients with AFDAS have a lower prevalence of risk factors, cardiovascular comorbidities, and structural heart disease than those with previously known AF, further contributing to a lower embolic risk profile.[33] Based on the interplay of cardiac monitoring duration, AF burden, and embolic risk, strictly applying the definition threshold of ≥24 hours monitoring for a diagnosis of ESUS and the resulting low proportion of patients receiving PCM before enrollment may have impacted the overall study results. The short pre-enrollment cardiac monitoring in all ESUS trials may have theoretically resulted in the diagnosis and resulting exclusion of patients with high-burden AF, who are the most likely to benefit from anticoagulation. Conversely, the 24-hour screening strategy may have resulted in the inclusion of patients with subclinical and lower-burden AF. Although ARCADIA sought to assess the benefit of anticoagulation in atrial cardiopathy in patients without AF (including AFDAS within the first 180 days), the latter selection bias may have led to the inclusion of a large proportion of patients with lower-risk AF, who were less likely to benefit from oral anticoagulation.[36]

The Future of Anticoagulation in ESUS and Atrial Cardiopathy Without AF

The neutral results of the ESUS trial raise questions about the concept of atrial cardiopathy and the optimal biomarkers (and their thresholds) to identify thrombogenic atrial substrate that would benefit from anticoagulation for stroke prevention. Perhaps it was too big a feat to prove within an RCT setting that atrial cardiopathy is a distinct, independent, and treatable entity all at the same time. The concept that atrial cardiopathy per se represents a residual risk of stroke recurrence attributable to an unrecognized cardiac source of embolism beyond detectable AF is in our opinion still valid. The first question is, if all patients with *any* degree of atrial cardiopathy alone without a coexisting relevant high risk of recurrence really benefit from oral anticoagulation. Then, the subsequent question is, how to best distinguish the threshold of atrial cardiopathy "disease burden" that both warrants a change in practice and leads to poorer outcomes.

Conceivably, the NT-proBNP level thresholds selected in ARCADIA were too broad to truly represent a high-risk atrial cardiopathy population. As mentioned previously, in WARSS, patients with increased NT-proBNP were associated with a lower risk of stroke recurrence when randomized to warfarin rather than aspirin.[17] However, the largest difference in 2-year probability of stroke or death among patients randomized to warfarin vs aspirin was shown at levels of NT-proBNP greater than approximately 750 pg/mL.[17] ARCADIA included patients with NT-proBNP of 250 pg/mL or more, representing about 61% of the study population, and may have been too low a threshold. Notably, there was no interaction between NT-proBNP levels dichotomized at a median of 303 pg/mL and treatment effect ($p = 082$). The fact that only ~1% of the study population had LA diameter index >3 cm/m^2, another marker of atrial cardiopathy, supports this hypothesis; this biomarker perhaps being the most specific to risk. Other limitations that might have contributed to the observed findings in ARCADIA include the choice of the biomarkers based on those that could be scaled to a large population, timing of randomization (e.g., higher AF burden may also occur early after stroke and these patients have been excluded from the trial) crossover to the apixaban arm once AF was detected, lost to follow-up, adherence to study medication, and withdrawal from the trial.

The question remains on how best to identify patients with high risk of cardiac thrombogenicity and stroke recurrence who, at the time of the stroke, have yet to be diagnosed with AF. The answer probably lies with a surrogate marker of these characteristics other than those investigated in ARCADIA or with higher thresholds (eFigure 1). The MOSES (Midregional Proatrial Natriuretic Peptide to Guide Secondary Stroke Prevention) trial is an ongoing biomarker-guided secondary prevention trial that aims to select exactly these high-risk patients (NCT03961334). The MOSES trial uses MR-proANP for patient selection, a biomarker that is specifically released by the atrium, implicated in the pathophysiology of AF development, and associated with AF and major adverse cardiovascular events after stroke.[37-39] Furthermore, the biomarker cutoff has been validated in several previous stroke populations to be highly associated with AF diagnosed after stroke using Holter ECG (i.e., probably high burden of AF) as well as with major adverse cardiovascular events within 1 year after stroke.[14-16,40] The design of the study differs from ARCADIA and ATTICUS further by the fact that the selection is not restricted to the ESUS population because an underlying high-risk cardiac source might

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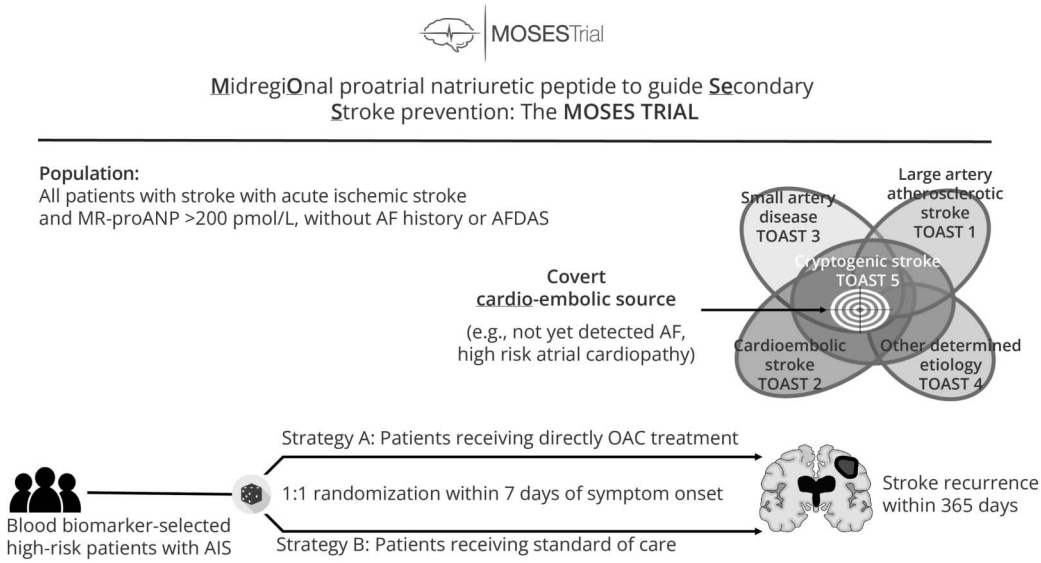
Figure 1 MOSES Trial Design


MOSESTrial
MidregiOnal proatrial natriuretic peptide to guide Secondary Stroke prevention: The MOSES TRIAL
Population:
All patients with stroke with acute ischemic stroke and MR-proANP >200 pmol/L, without AF history or AFDAS
Small artery disease TOAST 3
Large artery atherosclerotic stroke TOAST 1
Cryptogenic stroke TOAST 5
Covert cardio-embolic source
(e.g., not yet detected AF, high risk atrial cardiopathy)
Cardioembolic stroke TOAST 2
Other determined etiology TOAST 4
Strategy A: Patients receiving directly OAC treatment
1:1 randomization within 7 days of symptom onset
Strategy B: Patients receiving standard of care
Blood biomarker-selected high-risk patients with AIS
Stroke recurrence within 365 days

AF = atrial fibrillation; AFDAS = atrial fibrillation detected after stroke; AIS = acute ischemic stroke; MR-proANP = midregional proatrial natriuretic peptide; OAC = oral anticoagulation.

also be present in patients with strokes of other etiologies, such as large artery atherosclerosis or small vessel disease (Figure 1). Randomization takes place within 7 days of symptom onset (depending on lesion size) as recurrence rates are particularly high in the first days after stroke. Finally, the MOSES trial compares 2 treatment *strategies* rather than 2 drugs, that is, direct initiation of direct oral anticoagulant (DOAC) vs standard of care (typically antiplatelets if no other indication for anticoagulation is present, which would be an exclusion criteria). Through its study design and a different biomarker approach for selecting patients with high-risk atrial cardiopathy, the MOSES trial aims to offer new insights concerning biomarker-driven patient selection for secondary stroke prevention.

The Impact of NOAH-AFNET 6 and ARTESIA on Poststroke Cardiac Monitoring and Secondary Stroke Prevention Strategies

Over a decade ago, pivotal RCTs of poststroke cardiac monitoring demonstrated that PCM, either external or implantable, resulted in higher AF detection rates than standard-of-care monitoring.[41,42] As a result, there was a paradigm change with a progressive and steady uptake of intense poststroke cardiac rhythm monitoring. However, data from subsequent clinical trials and meta-analyses suggested that a more personalized approach to AF screening may be needed. Meta-analyses of RCTs of PCM have shown that longer duration of monitoring in patients with ischemic stroke or TIA is associated with increased initiation of anticoagulation, but not with lower stroke recurrence rates.[35,43] A meta-analysis of RCTs including 35,836 patients with and without stroke did show a small and marginally significant effect on stoke risk reduction associated with the use of PCM (RR 0.91, 95% CI 0.84–0.99).[44] Another meta-analysis of RCTs including 9,048 patients with and without stroke, with at least 1 vascular risk factor, showed that intense cardiac monitoring (>7 days) was associated with lower stroke risk (RR 0.76, 95% CI 0.59–0.96).[45] Considering these meta-analyses together, the lack of impact of PCM on stroke risk reduction may be explained by RCTs of cardiac monitoring in patients with stroke being underpowered because stroke recurrence was not the primary outcome and because of the modest effect size of the intervention. In addition, asymptomatic device-detected AF is heterogeneous, with a large proportion of low-burden AF and, as such, not as potent a stroke risk factor as symptomatic or ECG-detected AF.[36]

How do recent RCTs testing the efficacy and safety of anticoagulation in device-detected AF in high-risk populations affect the current landscape of secondary stroke prevention?

The NOAH-AFNET 6 (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) trial compared edoxaban 60 mg daily vs placebo or aspirin for preventing the composite outcome of stroke, systemic embolism, or cardiovascular death in 2,356 patients with AHRE.[46] A low dose of edoxaban was used in 28.7% of the active arm according to the European label (body weight ≤60 kg, a creatinine clearance of 15–50 mL/min, or concurrent use of strong P-glycoprotein inhibitors). The placebo group was assigned to double-dummy placebo and received a tablet containing either no active compound (46.1%) or aspirin

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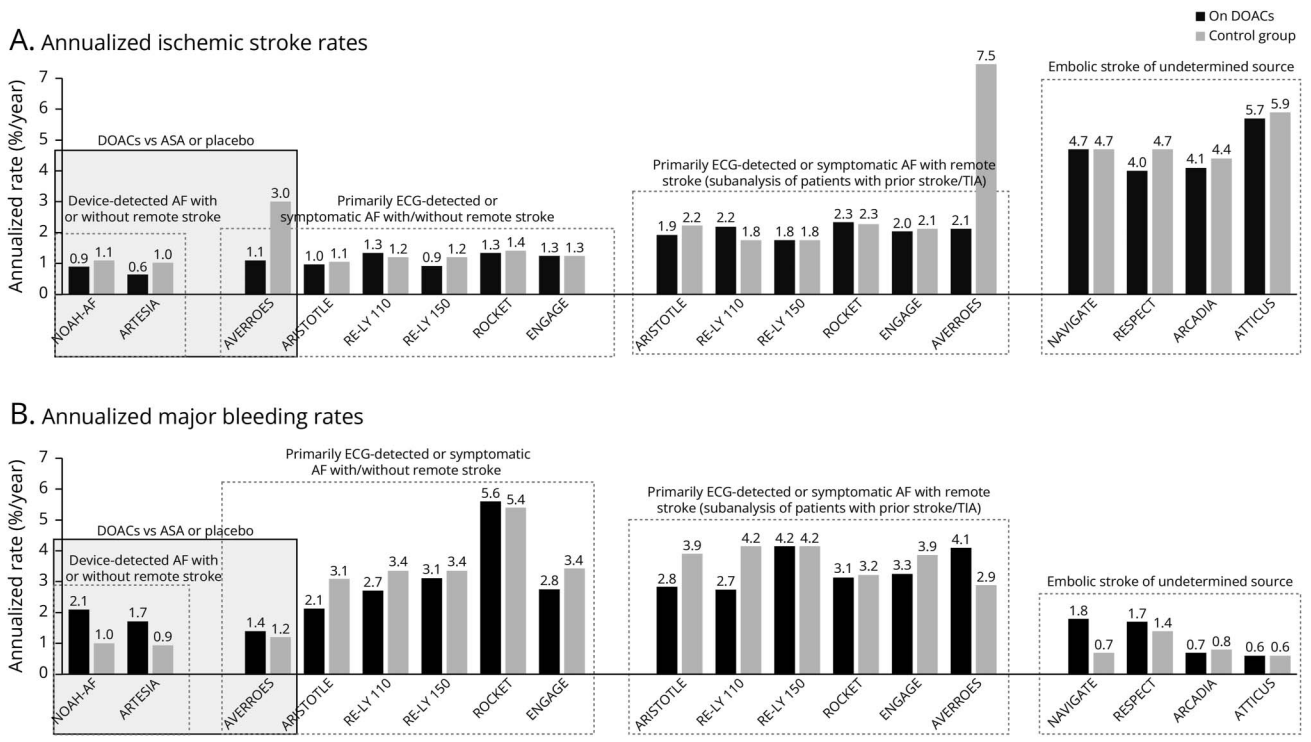
100 mg (53.9%) according to guideline-based indications for aspirin. NOAH-AFNET 6 was stopped prematurely at a median follow-up of 21 months because of safety concerns related to an excess of primary safety outcome events (composite of any-cause death or major bleeding) in the edoxaban group compared with the control arm (5.9% vs 4.5% per patient-year, HR 1.31, 95% CI 1.02–1.67) and futility for the efficacy of edoxaban for preventing the primary outcome (3.2% vs 4.0% per patient-year, HR 0.81, 95% 0.60–1.08). Rates of intracranial hemorrhage were not reported.

The ARTESIA (Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation) trial randomized 4,012 patients with subclinical atrial fibrillation (SCAF) lasting 6 minutes to 24 hours captured on an ICM or other cardiac implantable electronic devices to apixaban 5 mg twice daily vs aspirin 81 mg daily.[47] Of note, the term SCAF used in ARTESIA is equivalent to AHRE used in NOAH-AFNET 6 and designates asymptomatic paroxysms of irregular atrial tachycardia, likely but not confirmed to be AF. Patients were censored once an AF event lasted >24 hours or if the AF became symptomatic. After a mean follow-up of 3.5 years, 55 participants in the apixaban arm experienced a primary efficacy outcome event of stroke or systemic embolism compared with 86 patients in the aspirin group (0.78% vs 1.24% per patient-year; HR 0.63, 95% CI 0.45–0.88). Patients receiving apixaban had a higher rate of major bleeding than those receiving low-dose aspirin (Table 2). The risk of ischemic stroke and fatal or disabling stroke (HR 0.51, 95% CI 0.29–0.88), defined as a modified Rankin scale of 3–6, were also lower in the apixaban than in the aspirin group (Table 2). Symptomatic intracranial hemorrhage was reported in 12 patients with apixaban and 15 patients with aspirin (HR 0.73, 95% CI 0.39–1.36).[46]

In a study-level meta-analysis combining NOAH-AFNET 6 and ARTESIA data, the authors concluded that the results of both studies were consistent and pointed toward the same direction with an estimated absolute risk reduction in ischemic stroke of 3 per 1,000 patient-years and an estimated absolute risk increase for major bleeding of 7 per 1,000 patient-years.[48]

NOAH-AFNET 6 and ARTESIA provide the strongest evidence to date supporting the benefit of anticoagulation in patients with brief device-detected AF.[46,47] Several factors should be considered when analyzing the results of these trials from a secondary stroke prevention perspective and in the context of previous RCTs (Figure 2). First, NOAH-AFNET 6

Figure 2 Ischemic Stroke and Major Bleeding Rates in Recent Randomized Controlled Trials



(A) Annualized rates if acute ischemic stroke. (B) Annualized rates of major bleeding. NOAH-AFNET 6 compared edoxaban vs aspirin or placebo in patients with device-detected AF.[46] ARTESIA compared apixaban vs aspirin in patients with device-detected AF.[47] AVERROES compared apixaban vs aspirin in patients with primarily ECG-detected or symptomatic AF.[50] ARISTOTLE,[52] RE-LY,[53] ROCKET AF,[54] and ENGAGE AF[55] compared warfarin vs apixaban, dabigatran, rivaroxaban, and edoxaban, respectively. Data for patients with remote stroke or TIA in trials comparing direct oral anticoagulants vs warfarin and direct oral anticoagulants vs aspirin were reported in prespecified subanalyses from ARISTOTLE,[56] RE-LY,[57] ROCKET-AF,[58] ENGAGE AF,[59] and AVERROES.[60] NAVIGATE ESUS[2] and RE-SPECT ESUS[3] compared rivaroxaban vs aspirin and dabigatran vs aspirin, respectively, in patients with embolic stroke of undetermined source. ARCADIA and ATTICUS compared apixaban vs aspirin in patients with embolic stroke of undetermined source and atrial cardiopathy.[21,22]

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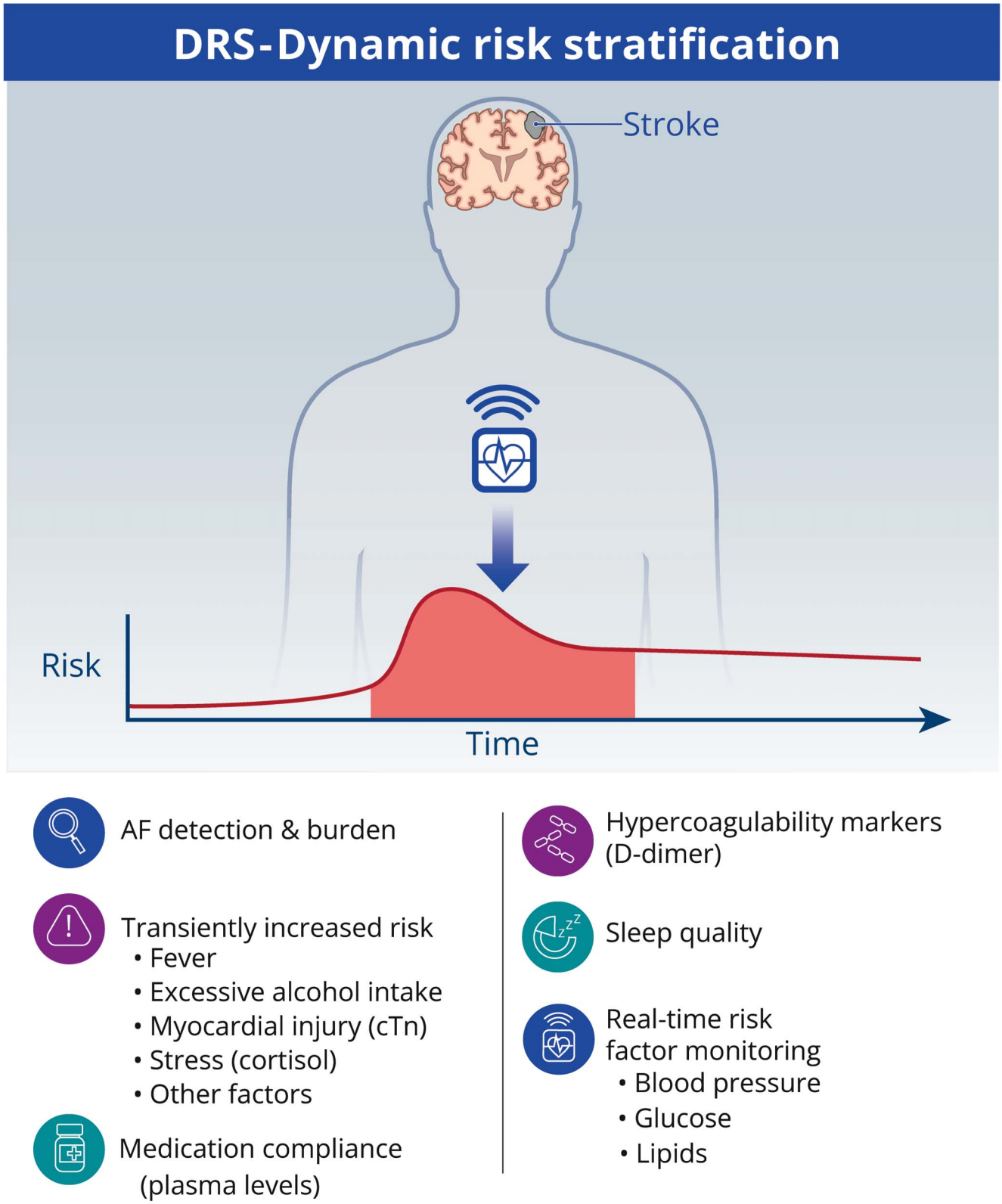
was stopped prematurely for safety concerns. As such, only 184 of the 220 planned primary efficacy outcome events had occurred at the end of the study follow-up, suggesting that NOAH-AFNET 6 was underpowered to confirm or rule out a modest reduction in the primary efficacy outcome of stroke or systemic embolism. Second, the annualized ischemic stroke

Figure 3 Dynamic Real-Time Stratification of Stroke Risk



AF = atrial fibrillation; Illustrated by Hannah Ahn.

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Table 3 Practical Considerations in the Evaluation of the Patient With ESUS

Potential causes of stroke in patients with ESUS	When to suspect
Nonstenotic carotid plaque (38%)[e1]	Nonstenotic (<50%) plaque with ulceration or adherent thrombus on CTA or Doppler US. Intraplaque hemorrhage on carotid wall MRI
Subclinical AF (25%)[e2]	Elevated BNP levels, left atrial enlargement, age
Cancer (9%)[e3]	Three-territory sign,[e6] constitutional symptoms, or elevated D-dimer
High-risk aortic plaque or thrombus (8%)[e4]	Mobile plaque or >4 mm on CTA or TEE
High-risk PFO (4%)[e5]	PASCAL classification: possible or probable[e7]

Abbreviations: AF = atrial fibrillation; BNP = brain natriuretic peptide; CTA = CT angiography; Doppler US = Doppler ultrasound; PFO = patent foramen ovale; TEE = transesophageal echocardiogram; PASCAL classification = PFO-Associated Stroke Causal Likelihood classification system; PASCAL possible = RoPE score <7 and high-risk PFO features (mobile interatrial septum or >20 microbubbles), or RoPE score ≥7 without high-risk PFO features; PASCAL probable = RoPE score ≥7 and high-risk PFO features; ROPE = Risk of Paradoxical Embolism.

rates in the anticoagulant antiplatelet/placebo arms of NOAH-AFNET 6 (1.10% per year) and ARTESIA (1.24% per year) are relatively low and support the notion that device-detected and asymptomatic AF are relatively low risk (Table 1, Figure 2).[49] As a reference, the annualized ischemic stroke risk in the aspirin arm of the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, which compared apixaban vs aspirin in patients with a predominance of ECG-detected AF, was 3% per year.[50] Third, the low risk of ischemic stroke among patients with device-detected AHRE or SCAF may partially explain why NOAH-AFNET 6 did not show a benefit of apixaban vs aspirin for preventing stroke or systemic embolism after being prematurely stopped. In addition, the low risk of ischemic stroke in the ARTESIA population may also explain why the absolute ischemic stroke risk reduction was only 0.38% per year in patients with apixaban compared with that in patients with aspirin. With the limitations of comparisons of studies with different population characteristics (Table 1), the absolute ischemic stroke risk reduction in AVERROES was 5-fold higher than that of ARTESIA (1.90% per year vs 0.38% per year). The latter supports the concept that, in general, the intensity of cardiac monitoring is inversely related to the detected AF-related ischemic stroke risk.[49] Fourth, the 62% higher risk of major bleeding in the DOAC vs aspirin/placebo in the study-level meta-analysis of NOAH-AFNET 6 and ARTESIA (HR 1.62, 95% CI 1.05–2.50) suggests that the benefit of preventing a small number of strokes may be partially outweighed by the risk of causing a major bleed. However, it must be noted that 45% of strokes in the aspirin group were fatal or disabling, whereas only 10% of patients with major hemorrhagic events in the apixaban arm died of bleeding or required immediate life-saving measures. Fifth, patients in ARTESIA had underlying cardiac conditions requiring cardiac implantable devices and pacemakers, which differs substantially from the general stroke population. In fact, only 5.2% of the ARTESIA study cohort received an ICM.[47] In summary, shared decision making incorporating patient age, functional status, and bleeding risk is advisable.

Conclusion

The studies mentioned in this review have helped clarify several issues that are useful in daily stroke prevention. First, the recurrent stroke rate for a patient with ESUS is about 4%–5% per year. Second, a finite proportion of patients with ESUS will develop AF, but tools to predict which patients with AF will benefit from anticoagulation and when need further refinement. Acute myocardial infarctions have clear triggers (exposure to cold temperatures, acute stress, etc), which help explain why an individual experiences a coronary event at a very specific moment. By contrast, there are not such triggers for ischemic strokes. As such, the occurrence of ischemic strokes at a specific timepoint in an individual lifetime is highly unpredictable. In the future, more sophisticated multiparametric implantable or external devices, capable of monitoring not only cardiac rhythm but also other factors known to dynamically affect long-term and immediate stroke risk (plasma levels of medications, sleep quality, fever/infections, plasma biomarkers, catecholamine levels, etc.), may be available. Artificial intelligence-driven devices with real-time analysis of the interplay of these variables (dynamic risk stratification concept) may be capable of predicting with high accuracy when an individual will be at imminent risk of stroke (Figure 3). Third, the current ESUS construct is likely too broad to identify a group of patients who will benefit from anticoagulation and is based on a diagnosis of exclusion. Nonstenotic carotid plaques, hypercoagulable states, aortic atheroma, cancer, and other conditions (not all responsive to anticoagulation) likely play an important role in ESUS-type strokes (Table 3).[51] As such, the search for underlying causes of ischemic stroke should be optimized by using advanced diagnostic procedures based on specific patients' characteristics. A further refinement or enrichment of study cohorts by selecting older patients (e.g., ≥75 years without excluding very older individuals) with other high-risk characteristics may prove beneficial in next-generation trials.

Several unresolved questions remain. These include the utility of new biomarkers, the identification of patients with

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asymptomatic device-detected AF of short duration who may or may not need anticoagulation, and the health economic implications of brief vs PCM. Addressing these topics will augment the clinician's ability to provide personalized stroke prevention.

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Michelle C. Johansen, MD, PhD, FAHA	Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content
Gian Marco De Marchis, MD, MSc	Kantonsspital St. Gallen, Department of Neurology & Stroke Center, St. Gallen and Department of Clinical Research, University of Basel, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content
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Urs Fischer, MD, MSc	Department of Neurology, University Hospital Basel, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content
Seemant Chaturvedi, MD	Department of Neurology & Stroke Program, University of Maryland School of Medicine, Baltimore	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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